

Remarks

Introduction

Receipt is acknowledged of the Office Action dated November 21, 2000. In the Action the Examiner has rejected claims 21-24 and 39-103 under alleged non-enablement. The Examiner has also rejected claims 21-24 and 39-103 as allegedly indefinite.

By the foregoing amendments, Applicants have amended claims 21-24 and no claims have been added or canceled. Consequently, claims 21-24 and 39-103 are pending for the Examiner's reconsideration. In this regard, reconsideration and withdrawal of the outstanding rejections in view of the foregoing amendments and remarks set forth below is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, first paragraph

On page 2 of the Office Action, the Examiner has rejected claims 21-24 and 39-103 under 35 U.S.C. § 112, first paragraph under alleged non-enablement. Specifically, the Examiner asserts that prophylaxis of several diseases recited in claims 23 and 24 is not disclosed. Applicants respectfully traverse the rejection.

Without acquiescing in the statements as set forth in the rejection, and solely for the purpose of expediting the instant application, Applicants have amended claim 23 to recite treating. One of ordinary skill in the art would understand "treating" to include the suppression of reoccurrence of diseases or disorders. An example would be the suppression of reoccurring instances of asthma attacks. Applicants have also amended claim 24 to recite "inhibiting adhesion and/or migration of leukocytes." No new matter is added with these amendments. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, second paragraph

On page 3 of the Office action, the Examiner has rejected claims 21-24 and 39-103 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants presume that the Examiner asserts that the definition "free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry" for R⁶ is indefinite. The Examiner also pointed out typographical error in claim 22.

Without acquiescing in the propriety of the rejection, and solely for the purpose of expediting prosecution of the instant application, Applicants have amended the definition of R⁶ in claims 21-24 to recite, in part, "optionally protected free functional groups."

Applicants submit that this term is clear to one of ordinary skill. Applicants have also made minor claim amendments to correct typographical errors. Applicants submit that the claims distinctly describe the instant invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing remarks, reconsideration of the application and allowance of all claims is requested. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the number below.

Respectfully submitted,

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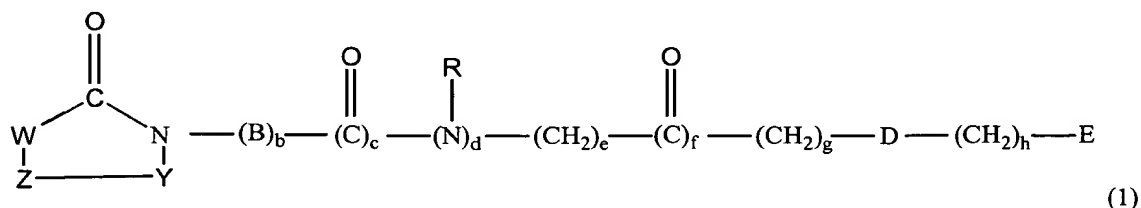
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21. **(Twice Amended)** A method for suppressing inflammation comprising administering to a subject in need thereof an effective amount of a preparation comprising an effective amount of at least one compound of the formula I:



in which

W is $\text{R}^1\text{-A-C(R}^{13})$ [\leq];

Y is a carbonyl;

Z is $\text{N(R}^0)$;

A is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₃-C₇)-cycloalkylene, phenylene, phenylene-(C₁-C₆)-alkyl, (C₁-C₆)-alkylenephenyl, phenylene-(C₂-C₆)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C₁-C₆) alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₂-C₆)-alkenylene, phenylene, phenylene-(C₁-C₃)-alkyl, (C₁-C₃)-alkylenephenyl, where the bivalent (C₁-C₆)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkyl-(C₁-C₆)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl-(C₁-C₆)-alkyl optionally substituted in the heteroaryl radical;

D is $\text{C(R}^2)(\text{R}^3)$, $\text{N(R}^3)$ or $\text{CH=C(R}^3)$;

E is R^{10}CO ;

- R is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, optionally substituted (C₆-C₁₄)-aryl or (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical;
- R⁰ is (C₃-C₁₂)-cycloalkyl, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl, (C₆-C₁₂)-bicycloalkyl, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-tricycloalkyl, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl-(C₁-C₈)-alkyl optionally substituted in the heteroaryl radical, CHO, (C₁-C₈)-alkyl-CO, (C₃-C₁₂)-cycloalkyl-CO, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-bicycloalkyl-CO, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-tricycloalkyl-CO, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-CO, optionally substituted (C₆-C₁₄)-aryl-CO, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl-(C₁-C₈)-alkyl-CO optionally substituted in the heteroaryl radical, (C₁-C₈)-alkyl-S(O)_n, (C₃-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-S(O)_n, optionally substituted (C₆-C₁₄)-aryl-S(O)_n, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-S(O)_n optionally substituted in the aryl radical, optionally substituted heteroaryl-S(O)_n or heteroaryl-(C₁-C₈)-alkyl-S(O)_n optionally substituted in the heteroaryl radical, where n is 1 or 2;
- R¹ is X-NH-C(=NH)-(CH₂)_n or X¹-NH-(CH₂)_n, where p is 0, 1, 2 or 3;
- X is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, optionally substituted (C₆-C₁₄)-arylcarbonyl, optionally substituted (C₆-C₁₄)-aryloxycarbonyl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl which can also be substituted in the aryl radical, (R⁸O)₂P(O), cyano, hydroxyl (C₁-C₆)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy which can also be substituted in the aryl radical, or amino;
- X¹ has one of the meanings of X or is R'-NH-C(=N-R''), where R' and R'' independently of one another have the meanings of X;
- R² is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R³ is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, (C₃-C₈)-cycloalkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₂-C₈)-alkenylcarbonyl, (C₂-C₈)-

alkynylcarbonyl, pyridyl, $R^{11}NH$, R^4CO , $COOR^4$, $CON(CH_3)R^{14}$, $CONHR^{14}$, $CSNHR^{14}$, $COOR^{15}$, $CON(CH_3)R^{15}$ or $CONHR^{15}$;

R^4 is hydrogen or (C_1-C_{28}) -alkyl which can optionally be mono- or polysubstituted by identical or different radicals $R^{4'}$; $R^{4'}$ is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di- $((C_1-C_{18})$ -alkyl)aminocarbonyl, amino- (C_2-C_{18}) -alkylaminocarbonyl, amino- (C_1-C_3) -alkylphenyl- (C_1-C_3) -alkylaminocarbonyl, (C_1-C_{18}) -alkylcarbonylamino- (C_1-C_3) -alkylphenyl- (C_1-C_3) -alkylaminocarbonyl, (C_1-C_{18}) -alkylcarbonylamino- (C_2-C_{18}) -alkylaminocarbonyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18}) -alkoxy, (C_1-C_{18}) -alkoxycarbonyl, optionally substituted (C_3-C_8) -cycloalkyl, halogen, nitro, trifluoromethyl or the radical R^5 ;

R^5 is optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur, a radical R^6 or a radical R^6CO- , where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or different radicals from the group consisting of (C_1-C_{18}) -alkyl, (C_1-C_{18}) -alkoxy, halogen, nitro, amino and trifluoromethyl;

R^6 is R^7R^8N , R^7O or R^7S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally $N-(C_1-C_8)$ -alkylated or $N-((C_6-C_{14})$ -aryl- (C_1-C_8) -alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to $-NH-CH_2-$, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place of **optionally protected free functional groups** **[free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry]**;

R^7 is hydrogen, (C_1-C_{18}) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl, (C_1-C_{18}) -alkoxycarbonyl, (C_1-C_{18}) -alkoxycarbonyl, (C_6-C_{14}) -arylcarbonyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkylcarbonyl or (C_6-C_{14}) -aryl- (C_1-C_{18}) -alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where

the aryl radicals can be mono- or polysubstituted, preferably monosubstituted by identical or different radicals from the group consisting of (C₁-C₈)-alkyl, (C₁-C₈)-alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally N-(C₁-C₈)-alkylated or N-((C₆-C₁₄)-aryl-(C₁-C₈)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CH₂-;

- R⁸ is hydrogen, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl which can also be substituted in the aryl radical;
- R⁹ is hydrogen, aminocarbonyl, (C₁-C₁₈)-alkylaminocarbonyl, (C₃-C₈)-cycloalkylaminocarbonyl, optionally substituted (C₆-C₁₄)-arylaminocarbonyl, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₃-C₈)-cycloalkyl;
- R¹⁰ is hydroxyl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹¹ hydrogen, (C₁-C₁₈)-alkyl, R¹²CO, optionally substituted (C₆-C₁₄)-aryl-S(O)₂, (C₁-C₁₈)-alkyl-S(O)₂, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or R⁹NHS(O)₂;
- R¹² is hydrogen, (C₁-C₁₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, optionally substituted (C₆-C₁₄)-aryl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹³ is hydrogen, (C₁-C₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R¹⁴ is hydrogen or (C₁-C₂₈)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl)-aminocarbonyl, amino-(C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonyl-amino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₃-C₈)-cycloalkyl, HOS(O)₂-(C₁-

C₃)-alkyl, R⁹NHS(O)₂-(C₁-C₃)-alkyl, (R⁸O)₂P(O)-(C₁-C₃)-alkyl, tetrazolyl-(C₁-C₃)-alkyl, halogen, nitro, trifluoromethyl and R⁵;

R¹⁵ is R¹⁶-(C₁-C₆)-alkyl or R¹⁶;

R¹⁶ is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by one or more identical or different substituents from the group consisting of (C₁-C₄)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

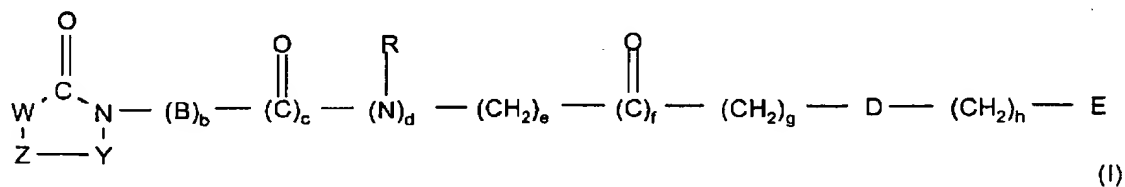
f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.

22. **(Twice Amended)** A method for antagonizing VLA-4 comprising administering to a subject in need thereof an effective amount of a preparation comprising an effective amount of at least one compound of the formula I:



in which

W is R¹-A-C(R¹³) [<];

Y is a carbonyl;

Z is N(R⁰);

A is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₃-C₇)-cycloalkylene, phenylene, phenylene-(C₁-C₆)-alkyl, (C₁-C₆)-alkylenophenyl, phenylene-(C₂-C₆)-alkenyl or a bivalent radical of a 5- or 6-membered

- saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C₁-C₆)-alkyl or doubly bonded oxygen or sulfur;
- B is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₂-C₆)-alkenylene, phenylene, phenylene-(C₁-C₃)-alkyl, (C₁-C₃)-alkylenephenyl, where the bivalent (C₁-C₆)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkyl-(C₁-C₆)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl-(C₁-C₆)-alkyl, optionally substituted in the heteroaryl radical;
- D is C(R²)(R³), N(R³) or CH=C(R³);
- E is R¹⁰CO;
- R is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, optionally substituted (C₆-C₁₄)-aryl or -(C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical;
- R⁰ is (C₃-C₁₂)-cycloalkyl, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl, (C₆-C₁₂)-bicycloalkyl, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl, (C₆-C₁₂)-tricycloalkyl, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl-(C₁-C₈)-alkyl optionally substituted in the heteroaryl radical, CHO, (C₁-C₈)-alkyl-CO, (C₃-C₁₂)-cycloalkyl-CO, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-bicycloalkyl-CO, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-tricycloalkyl-CO, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-CO, optionally substituted (C₆-C₁₄)-aryl-CO, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl-(C₁-C₈)-alkyl-CO optionally substituted in the heteroaryl radical, (C₁-C₈)-alkyl-S(O)_n, (C₃-C₁₂)-cycloalkyl-S(O)_n, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl-S(O)_n, (C₆-C₁₂)-bicycloalkyl-S(O)_n, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl-S(O)_n, (C₆-C₁₂)-tricycloalkyl-S(O)_n, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-S(O)_n, optional substituted (C₆-C₁₄)-aryl-S(O)_n, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-S(O)_n, optionally substituted in the aryl radical, optionally substituted heteroaryl-S(O)_n or heteroaryl-(C₁-C₈)-alkyl-S(O)_n optionally substituted in the heteroaryl radical, where n is 1 or 2;
- R¹ is X-NH-C(=NH)-(CH₂)_p or X¹-NH-(CH₂)_p, where p is 0, 1, 2 or 3;

- X is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, optionally substituted (C₆-C₁₄)-arylcarbonyl, optionally substituted (C₆-C₁₄)-aryloxycarbonyl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl which can also be substituted in the aryl radical, (R⁸O)₂P(O), cyano, hydroxyl, (C₁-C₆)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy which can also be substituted in the aryl radical, or amino;
- X¹ has one of the meanings of X or is R'-NH-C(=N-R''), where R' and R'' independently of one another have the meanings of X;
- R² is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R³ is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, (C₃-C₈)-cycloalkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₂-C₈)-alkenylcarbonyl, (C₂-C₈)-alkynylcarbonyl, pyridyl, R¹¹NH, R⁴CO, COOR⁴, CON(CH₃)R¹⁴, CONHR¹⁴, CSNHR¹⁴, COOR¹⁵, CON(CH₃)R¹⁵ or CONHR¹⁵;
- R⁴ is hydrogen or (C₁-C₂₈)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals R^{4'}; R^{4'} is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl)aminocarbonyl, amino-(C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, -(C₂-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted -(C₃-C₈)-cycloalkyl, halogen, nitro, trifluoromethyl or the radical R⁵;
- R⁵ is optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur, a radical R⁶ or a radical R⁶CO, where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or

- different radicals from the group consisting of (C₁-C₁₈)-alkyl, (C₁-C₁₈)-alkoxy, halogen, nitro, amino and trifluoromethyl;
- R⁶ is R⁷R⁸N, R⁷O or R⁷S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally N-(C₁-C₈)-alkylated or N-((C₆-C₁₄)-aryl-(C₁-C₁₈)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CR₂-, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place of **optionally protected free functional groups** **[free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry]**;
- R⁷ is hydrogen, (C₁-C₁₈)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl, (C₁-C₁₈)-alkylcarbonyl, (C₁-C₁₈)-alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkylcarbonyl or (C₆-C₁₄)-aryl-(C₁-C₁₈)-alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably monosubstituted, by identical or different radicals from the group consisting of (C₁-C₈)-alkyl, (C₁-C₈)-alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally N-(C₁-C₈)-alkylated or N-((C₆-C₁₄)-aryl-(C₁-C₈)-alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to -NH-CH₂-;
- R⁸ is hydrogen, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl which can also be substituted in the aryl radical;
- R⁹ is hydrogen, aminocarbonyl, (C₁-C₁₈)-alkylaminocarbonyl, (C₃-C₈)-cycloalkylaminocarbonyl, optionally substituted (C₆-C₁₄)-arylaminocarbonyl, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₃-C₈)-cycloalkyl;
- R¹⁰ is hydroxyl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹¹ is hydrogen, (C₁-C₁₈)-alkyl, R¹²CO, optionally substituted (C₆-C₁₄)-aryl-S(O)₂, (C₁-C₁₈)-alkyl-S(O)₂, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or R⁹NHS(O)₂;

- R¹² is hydrogen, (C₁-C₁₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, optionally substituted (C₆-C₁₄)-aryl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹³ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R¹⁴ is hydrogen or (C₁-C₂₈)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl)-aminocarbonyl, amino-(C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonyl-amino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₃-C₈)-cycloalkyl, HOS(O)₂-(C₁-C₃)-alkyl, R⁹NHS(O)₂-(C₁-C₃)-alkyl, (R⁸O)₂P(O)-(C₁-C₃)-alkyl, tetrazolyl-(C₁-C₃)-alkyl, halogen, nitro, trifluoromethyl and R⁵;
- R⁵ is R¹⁶-(C₁-C₆)-alkyl or R¹⁶;
- R¹⁶ is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by one or more **identical** [identifical] or different substituents from the group consisting of (C₁-C₄)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

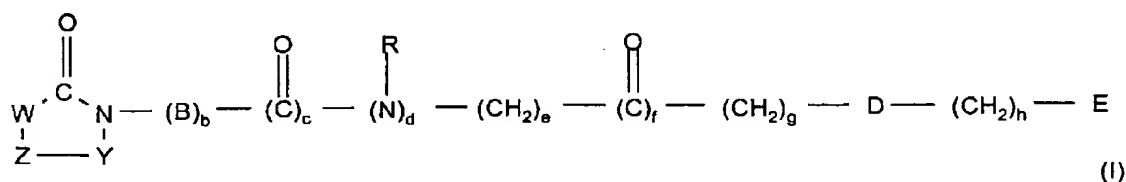
f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.

23. **(Twice Amended)** A method for treating **[or preventing]** a disease or disorder selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, inflammatory disorders of the central nervous system, asthma, allergies, cardiovascular disorders, atherosclerosis, restenoses, diabetes, damage to organ transplants, tumor growth, tumor metastasis, and malaria comprising administering to a subject in need thereof an effective amount of a preparation comprising an effective amount of at least one compound of the formula I:



in which

W is R'-A-C(R¹³) [\leq];

Y is a carbonyl;

Z is N(R⁰);

A is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₃-C₇)-cycloalkylene, phenylene, phenylene-(C₁-C₆)-alkyl, (C₁-C₆)-alkylenephenyl, phenylene-(C₂-C₆)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C₁-C₆)-alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₂-C₆)-alkenylene, phenylene, phenylene-(C₁-C₃)-alkyl, (C₁-C₃)-alkylenephenyl, where the bivalent (C₁-C₆)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₁₀)-cycloalkyl-(C₁-C₆)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl (C₁-C₆)-alkyl optionally substituted in the heteroaryl radical;

D is C(R²)(R³), N(R³) or CH=C(R³);

- E is $R^{10}CO$;
- R is hydrogen, (C_1-C_8) -alkyl, (C_3-C_8) -cycloalkyl, optionally substituted (C_6-C_{14}) -aryl or (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical;
- R^0 is (C_3-C_{12}) -cycloalkyl, (C_3-C_{12}) -cycloalkyl- (C_1-C_8) -alkyl, (C_6-C_{12}) -bicycloalkyl, (C_6-C_{12}) -bicycloalkyl- (C_1-C_8) -alkyl, (C_6-C_{12}) -tricycloalkyl, (C_6-C_{12}) -tricycloalkyl- (C_1-C_8) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl- (C_1-C_8) -alkyl optionally substituted in the heteroaryl radical, CHO, (C_1-C_8) -alkyl-CO, (C_3-C_{12}) -cycloalkyl-CO, (C_3-C_{12}) -cycloalkyl- (C_1-C_8) -alkyl-CO, (C_6-C_{12}) -bicycloalkyl-CO, (C_6-C_{12}) -bicycloalkyl- (C_1-C_8) -alkyl-CO, (C_6-C_{12}) -tricycloalkyl-CO, (C_6-C_{12}) -tricycloalkyl- (C_1-C_8) -alkyl-CO, optionally substituted (C_6-C_{14}) -aryl-CO, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl- (C_1-C_8) -alkyl-CO optionally substituted in the heteroaryl radical, (C_1-C_8) -alkyl-S(O)_n, (C_3-C_{12}) -cycloalkyl-S(O)_n, (C_3-C_{12}) -cycloalkyl- (C_1-C_8) -alkyl-S(O)_n, (C_6-C_{12}) -bicycloalkyl-S(O)_n, (C_6-C_{12}) -bicycloalkyl- (C_1-C_8) -alkyl-S(O)_n, (C_6-C_{12}) -tricycloalkyl-S(O)_n, (C_6-C_{12}) -tricycloalkyl- (C_1-C_8) -alkyl-S(O)_n, optionally substituted (C_6-C_{14}) -aryl-S(O)_n, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl-S(O)_n optionally substituted in the aryl radical, optionally substituted heteroaryl-S(O)_n or heteroaryl- (C_1-C_8) -alkyl-S(O)_n optionally substituted in the heteroaryl radical, where n is 1 or 2;
- R^1 is X-NH-C(=NH)-(CH₂)_p or X¹-NH-(CH₂)_p, where p is 0, 1, 2 or 3;
- X is hydrogen, (C_1-C_6) -alkyl, (C_1-C_6) -alkylcarbonyl, (C_1-C_6) -alkoxycarbonyl, (C_1-C_{18}) -alkylcarbonyloxy, (C_1-C_6) -alkoxycarbonyl, optionally substituted (C_6-C_{14}) -arylcarbonyl, optionally substituted (C_6-C_{14}) -aryloxycarbonyl, (C_6-C_{14}) -aryl- (C_1-C_6) -alkoxycarbonyl which can also be substituted in the aryl radical, $(R^8O)_2P(O)$, cyano, hydroxyl, (C_1-C_6) -alkoxy, (C_6-C_{14}) -aryl- (C_1-C_6) -alkoxy which can also be substituted in the aryl radical, or amino;
- X^1 has one of the meanings of X or is R'-NH-C(=N-R''), where R' and R'' independently of one another have the meanings of X;
- R^2 is hydrogen, (C_1-C_8) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical or (C_3-C_8) -cycloalkyl;

- R^3 is hydrogen, (C_1-C_8) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical, (C_3-C_8) -cycloalkyl, (C_2-C_8) -alkenyl, (C_2-C_8) -alkynyl, (C_2-C_8) -alkenylcarbonyl, (C_2-C_8) alkynylcarbonyl, pyridyl, $R^{11}NH$, R^4CO , $COOR^4$, $CON(CH_3)R^{14}$, $CONHR^{14}$, $CSNHR^{14}$, $COOR^{15}$, $CON(CH_3)R^{15}$ or $CONHR^{15}$;
- R^4 is hydrogen or (C_1-C_{28}) -alkyl which can optionally be mono- or polysubstituted by identical or different radicals $R^{4'}$; $R^{4'}$ is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di- $((C_1-C_{18}))$ -alkyl)aminocarbonyl, amino- (C_2-C_{18}) -alkylaminocarbonyl, amino- (C_1-C_3) -alkylphenyl- (C_1-C_3) -alkylaminocarbonyl, (C_1-C_{18}) -alkylcarbonylamino- (C_1-C_3) -alkylphenyl- (C_1-C_3) -alkylaminocarbonyl, (C_1-C_{18}) -alkylcarbonylamino- (C_2-C_{18}) -alkylaminocarbonyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C_1-C_{18}) -alkoxy, (C_1-C_{18}) alkoxycarbonyl, optionally substituted (C_3-C_8) -cycloalkyl, halogen, nitro, trifluoromethyl or the radical R^5 ;
- R^5 is optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur, a radical R^6 or a radical R^6CO- . where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or different radicals from the group consisting of (C_1-C_{18}) -alkyl, (C_1-C_{18}) -alkoxy, Halogen, nitro, amino and trifluoromethyl;
- R^6 is R^7R^8N , R^7O or R^7S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally $N-(C_1-C_8)$ -alkylated or $N-((C_6-C_{14})$ -aryl- (C_1-C_8) -alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to $-NH-CH_2-$, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place **optionally protected free functional groups** [free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry];

- R^7 is hydrogen, (C_1-C_{18}) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl, (C_1-C_{18}) -alkylcarbonyl, (C_1-C_{18}) -alkoxycarbonyl, (C_6-C_{14}) -arylcarbonyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkylcarbonyl or (C_6-C_{14}) -aryl- (C_1-C_{18}) -alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably monosubstituted, by identical or different radicals from the group consisting of (C_1-C_8) -alkyl, (C_1-C_8) -alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally N- (C_1-C_8) -alkylated or N- $((C_6-C_{14})$ -aryl- (C_1-C_8) -alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to $-NH-CH_2-$;
- R^8 is hydrogen, (C_1-C_{18}) -alkyl, optionally substituted (C_6-C_{14}) -aryl or (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl which can also be substituted in the aryl radical;
- R^9 is hydrogen, aminocarbonyl, (C_1-C_{18}) -alkylaminocarbonyl, (C_3-C_8) -cycloalkylaminocarbonyl, optionally substituted (C_6-C_{14}) -arylaminocarbonyl, (C_1-C_{18}) -alkyl, optionally substituted (C_6-C_{14}) -aryl or (C_3-C_8) -cycloalkyl;
- R^{10} is hydroxyl, (C_1-C_{18}) -alkoxy, (C_6-C_{14}) -aryl- (C_1-C_8) -alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14}) -aryloxy, amino or mono- or di- $((C_1-C_{18})$ -alkyl)amino;
- R^{11} is hydrogen (C_1-C_{18}) -alkyl, $R^{12}CO$, optionally substituted (C_6-C_{14}) -aryl-S(O)₂, (C_1-C_{18}) -alkyl-S(O)₂, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical or $R^9NHS(O)_2$;
- R^{12} is hydrogen (C_1-C_{18}) -alkyl, (C_2-C_8) -alkenyl, (C_2-C_8) -alkynyl, optionally substituted (C_6-C_{14}) -aryl, (C_1-C_{18}) -alkoxy, (C_6-C_{14}) -aryl- (C_1-C_8) -alkoxy which can also be substituted in the aryl radical, optionally substituted (C_6-C_{14}) -aryloxy, amino or mono- or di- $((C_1-C_{18})$ -alkyl)amino;
- R^{13} is hydrogen, (C_1-C_6) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical or (C_3-C_8) -cycloalkyl;
- R^{14} is hydrogen or (C_1-C_{28}) -alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di- $((C_1-C_{18})$ -alkyl)-aminocarbonyl, amino- (C_2-C_{18}) -alkylaminocarbonyl, amino- (C_1-C_3) -alkylphenyl- (C_1-C_3) -alkylaminocarbonyl, (C_1-C_{18}) -alkylcarbonylamino- $(C_1-$

(C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonyl-amino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₁₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₃-C₈)-cycloalkyl, HOS(O)₂-(C₁-C₃)-alkyl, R⁹NHS(O)₂-(C₁-C₃)-alkyl, (R⁸O)₂P(O)-(C₁-C₃)-alkyl, tetrazolyl-(C₁-C₃)-alkyl, halogen, nitro, trifluoromethyl and R⁵,

R¹⁵ is R¹⁶-(C₁-C₆)-alkyl or R¹⁶;

R¹⁶ is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by one or more identical or different substituents from the group consisting of (C₁-C₄)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

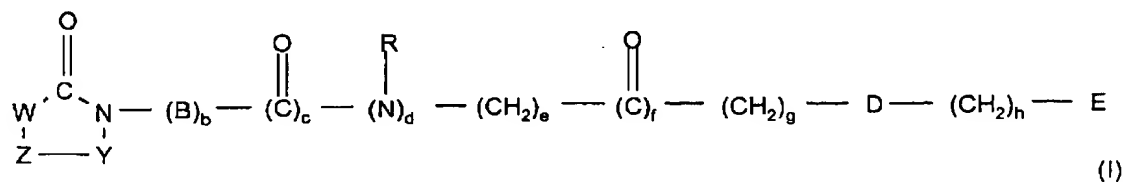
f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.

24. (Twice Amended) A method for inhibiting adhesion and/or migration of leukocytes in [for the treatment or prophylaxis of] diseases in which leucocyte adhesion and/or migration exhibits an undesired extent comprising administering to a subject in need thereof an effective amount of a preparation comprising an effective amount of at least one



compound of the formula I:

in which

W is R¹-A-C(R¹³) [\leq];

- Y is a carbonyl;
- Z is $N(R^0)$;
- A is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₃-C₇)-cycloalkylene, phenylene, phenylene-(C₁-C₆)-alkyl, (C₁-C₆)-alkylenephenyl, phenylene-(C₂-C₆)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C₁-C₆)-alkyl or doubly bonded oxygen or sulfur;
- B is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₂-C₆)-alkenylene, phenylene, phenylene-(C₁-C₃)-alkyl, (C₁-C₃)-alkyl, (C₁-C₃)-alkylenephenyl, where the bivalent (C₁-C₆)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkyl-(C₁-C₆)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl-(C₁-C₆)-alkyl optionally substituted in the heteroaryl radical;
- D is $C(R^2)(R^3)$, $N(R^3)$ or $CH=C(R^3)$;
- E is $R^{10}CO$;
- R is hydrogen, (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, optionally substituted (C₆-C₁₄)-aryl or (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical;
- R⁰ is (C₃-C₁₂)-cycloalkyl, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl, (C₆-C₁₂)-bicycloalkyl, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl, (C₆-C₁₂)-tricycloalkyl, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl-(C₁-C₈)-alkyl optionally substituted in the heteroaryl radical, CHO, (C₁-C₈)-alkyl-CO, (C₃-C₁₂)-cycloalkyl-CO, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-bicycloalkyl-CO, (C₆-C₁₂)-bicycloalkyl-(C₁-C₈)-alkyl-CO, (C₆-C₁₂)-tricycloalkyl-CO, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-CO, optionally substituted (C₆-C₁₄)-aryl-CO, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl-(C₁-C₈)-alkyl-CO optionally substituted in the heteroaryl radical, (C₁-C₈)-alkyl-S(O)_n, (C₃-C₁₂)-cycloalkyl-S(O)_n, (C₃-C₁₂)-cycloalkyl-(C₁-C₈)-alkyl-S(O)_n, (C₆-C₁₂)-bicycloalkyl-S(O)_n, (C₆-C₁₂)-

bicycloalkyl-(C₁-C₈)-alkyl-S(O)_n, (C₆-C₁₂)-tricycloalkyl-S(O)_n, (C₆-C₁₂)-tricycloalkyl-(C₁-C₈)-alkyl-S(O)_n, optionally substituted (C₆-C₁₄)-aryl-S(O)_n, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl-S(O)_n optionally substituted heteroaryl-S(O)_n or heteroaryl-(C₁-C₈)-alkyl-S(O)_n optionally substituted in the heteroaryl radical, where n is 1 or 2;

- R¹ is X-NH-C(=NH)-(CH₂)_p or X¹-NH-(CH₂)_p, where p is 0, 1, 2 or 3;
- X is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₁₈)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl, optionally substituted (C₆-C₁₄)-arylcarbonyl, optionally substituted (C₆-C₁₄)-aryloxycarbonyl, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxycarbonyl which can also be substituted in the aryl radical. (R⁸O)₂P(O), cyano, hydroxyl, (C₁-C₆)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₆)-alkoxy which can also be substituted in the aryl radical, or amino;
- X¹ has one of the meanings of X or is R'-NH-C(=N-R''), where R' and R'' independently of one another have the meanings of X;
- R² is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R³ is hydrogen, (C₁-C₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, (C₃-C₈)-cycloalkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₂-C₈)-alkenylcarbonyl, (C₂-C₈)-alkynylcarbonyl, pyridyl, R¹¹NH, R⁴CO, COOR⁴, CON(CH₃)R¹⁴, CONHR¹⁴, CSNHR¹⁴, COOR¹⁵, CON(CH₃)R¹⁵ or CONHR¹⁵;
- R⁴ is hydrogen or (C₁-C₂₈)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals R^{4'}; R^{4'} is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl)aminocarbonyl, amino-(C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₃-C₈)-cycloalkyl, halogen, nitro, trifluoromethyl or the radical R⁵;
- R⁵ is optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical, a mono- or bicyclic 5- to 12-membered

heterocyclic ring which can be aromatic, partially hydrogenated or completely hydrogenated and which can contain one, two or three identical or different heteroatoms from the group consisting of nitrogen,, oxygen and sulfur, a radical R^6 or a radical R^6CO- , where the aryl radical and, independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical or different radicals from the group consisting of (C_1-C_{18}) -alkyl, (C_1-C_{18}) -alkoxy, halogen, nitro, amino and trifluoromethyl;

R^6 is R^7R^8N , R^7O or R^7S or an amino acid side chain, a natural or unnatural amino acid, imino acid, optionally $N-(C_1-C_8)$ -alkylated or $N-((C_6-C_{14})$ -aryl- (C_1-C_8) -alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to $-NH-CH_2-$, and their esters and amides, where hydrogen or hydroxymethyl can optionally stand in place of **optionally protected free functional groups** [free functional groups and/or where free functional groups can be protected by protective groups customary in peptide chemistry];

R^7 is hydrogen, (C_1-C_{18}) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl, (C_1-C_{18}) -alkylcarbonyl, (C_1-C_{18}) -alkoxycarbonyl, (C_6-C_{14}) -arylcarbonyl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkylcarbonyl or (C_6-C_{14}) -aryl- (C_1-C_{18}) -alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably monosubstituted, by identical or different radicals from the group consisting of (C_1-C_8) -alkyl, (C_1-C_8) -alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or unnatural amino acid, imino acid, optionally $N-(C_1-C_8)$ -alkylated or $N-((C_6-C_{14})$ -aryl- (C_1-C_8) -alkylated) azaamino acid or a dipeptide radical which can also be substituted in the aryl radical and/or in which the peptide bond can be reduced to $-NH-CH_2-$;

R^8 is hydrogen, (C_1-C_{18}) -alkyl, optionally substituted (C_6-C_{14}) -aryl or (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl which can also be substituted in the aryl radical;

R^9 is hydrogen, aminocarbonyl, (C_1-C_{18}) -alkylaminocarbonyl, (C_3-C_8) -cycloalkylaminocarbonyl, optionally substituted (C_6-C_{14}) -arylaminocarbonyl, (C_1-C_{18}) -alkyl, optionally substituted (C_6-C_{14}) -aryl or (C_3-C_8) -cycloalkyl;

- R¹⁰ is hydroxyl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹¹ is hydrogen, (C₁-C₁₈)-alkyl, R¹²CO, optionally substituted (C₆-C₁₄)-aryl-S(O)₂, (C₁-C₁₈)-alkyl-S(O)₂, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or R⁹NHS(O)₂;
- R¹² is hydrogen, (C₁-C₁₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, optionally substituted (C₆-C₁₄)-aryl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl, (C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;
- R¹³ is hydrogen, (C₁-C₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;
- R¹⁴ is hydrogen or (C₁-C₂₈)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl-aminocarbonyl, amino-((C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₄)-alkylphenyl-(C₁-C₄)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-(C₁-C₃)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonyl-amino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₃-C₈)-cycloalkyl, HOS(O)₂-(C₁-C₃)-alkyl, R⁹NHS(O)₂-(C₁-C₃)-alkyl, (R⁸O)₂P(O)-(C₁-C₃)-alkyl, tetrazolyl-(C₁-C₃)-alkyl, halogen, nitro, trifluoromethyl and R⁵;
- R¹⁵ is R¹⁶-(C₁-C₆)-alkyl or R¹⁶;
- R¹⁶ is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by one or more identical or different substituents from the group consisting of (C₁-C₄)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their
physiologically tolerable salts.